REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-9 and 33-48, the only claims pending and currently under examination in this application.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 1-9 and 33-48 are rejected under 35 USC § 103(a) as allegedly being obvious over Cantor et al. (WO 99/22025, published May 6, 1999) (hereinafter "Cantor") in view of Baldeschwieler et al. (WO 95/25116, published September 21,1995) (hereinafter "Baldeschwieler"). The Applicants respectfully traverse the rejection.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a). *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). In order to meet its burden, the Office must first demonstrate that the prior art teaches or suggests all the claimed limitations. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

Independent Claims 1, 4, and 33 recite as follows:

> Claim 1: "producing a degenerate biopolymer feature location on said surface of said substrate by a method comprising providing a mixture of *two or more* different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions;"

> Claim 4: "producing a degenerate biopolymer feature location on said surface of said substrate by a method comprising: providing a mixture of *two or more* different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions;" and

> Claim 33: "producing a degenerate biopolymer feature location on said surface of said substrate by a method comprising: dispensing from a

dispensing system in at least one round of multiple rounds of subunit additions a mixture comprising a predetermined ratio of *two or more* different biopolymer subunit precursors."

The Office interprets the phrase "two or more different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions" to mean that the "two or more different biopolymer subunit precursors" need not be deposited to a feature location at once, but can be applied in more than a single round, such as a second round, third round, etc. (Office Action, page 5).

The Applicants respectfully disagree with this interpretation and submit that the claims clearly require that *a mixture* of two or more different biopolymer subunit precursors is provided (or dispensed) to a feature location in *one round* of multiple rounds of subunit additions. The use of the term "at least" indicates that such a *mixture* can also be provided (or dispensed) in additional rounds thereby creating additional sites of degeneracy, however, it must be provided (or dispensed) in one round.

This construction of the claim is consistent with the specification which includes the following exemplary description:

> The synthesis is achieved in accordance with the present invention by dispensing nucleotide precursors at the feature site so that, after the addition of nucleotide precursor corresponding to G at position 4, a mixture of nucleotide precursors corresponding to C, G, A and T is dispensed at position 5 in the next round of additions. To this end an additional reservoir and corresponding nozzle are included in the dispensing system. The additional reservoir contains all four of the above nucleotide precursors in a predetermined ratio, which is dispensed to the feature site using the additional nozzle. Alternatively, existing reservoirs each containing one of the four nucleotide precursors may be employed to dispense predetermined amounts of the nucleotide precursors to the feature site to form the mixture. In this latter approach activator should be added subsequent to depositing the complete mixture of nucleotide precursors.

(Specification, page 27).

Thus, regardless of whether the "mixture" is provided from a single nozzle or multiple nozzles, it is provided in one round of multiple rounds of subunit additions. As properly interpreted in view of the specification, the claims require that the

mixture be provided (or dispensed) to a feature location in *one round* of multiple rounds of subunit additions.

When the cited art is analyzed in view of the claims as properly interpreted, it is clear that the proposed art combination fails to render the claims *prima facie* obvious.

As best understood by the Applicants, it is the position of the Office that Cantor discloses a microarray comprising a plurality of degenerate oligonucleotides, said degenerate oligonucleotides comprising at least one degenerate nucleotide. The Office acknowledges that Cantor does not teach a particular method of fabricating such an array. However, the Office asserts that one of ordinary skill in the art would have clearly recognized various methods for fabricating a microarray at the time the invention was made, including the method disclosed by Baldeschwieler.

According to the Office, Baldeschwieler discloses a method of fabricating an array via use of an inkjet technology, wherein the method involves the attachment of molecules onto a substrate surface, for sequential synthesis of polynucleotides, wherein the reagents are dispensed from a microdrop dispensing device. The Office acknowledges that Baldeschwieler does not teach that a “mixture” of different biopolymer subunit precursors is provided during at least one round of multiple rounds of subunit additions. However, the Office asserts that one of ordinary skill in the art would have recognized that when “growing” a degenerate polynucleotide probe on an array’s surface, series of dimer additions could be utilized in addition to rounds of monomer additions. According to the Office, the deposition of dimers in fabricating the array of Cantor by the method disclosed in Baldeschwieler would have resulted in the invention as claimed.

The Applicants submit that the proposed combination of Cantor and Baldeschwieler fails to teach or suggest all the elements of independent Claims 1, 4 and 33. Specifically, the combined references fail to teach or suggest *providing (or dispensing) a mixture of two or more different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions.*

The Office acknowledges that these elements are not taught by Cantor (Office Action, page 3). In fact, Cantor contains no description whatsoever regarding the actual creation of the described array. Instead, Cantor describes a simulated laboratory experiment in which a single stranded DNA of unknown sequence is sheared into overlapping oligomers 16 bases long and "hybridized" to a theoretical set of 25 "degenerate" probe groups (Cantor, page 6, lines 12 – 22). This complete lack of teaching and silence regarding the claimed elements cannot be construed as a suggestion to include the step of providing (or dispensing) a mixture of two or more different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions.

In an attempt to remedy the acknowledged deficiencies of Cantor, the Office relies on the addition of Baldeschwieler. As indicated above, the Office acknowledges that Baldeschwieler does not teach that a mixture of different biopolymer subunit precursors is provided during at least one round of multiple rounds of subunit additions. Without providing support, the Office simply asserts that one of ordinary skill in the art would have recognized that when "growing" a degenerate polynucleotide probe on an array's surface, a series of dimer additions could be utilized in addition to rounds of monomer additions. However, even if a person of ordinary skill in art were to utilize a series of dimer additions to create an array comprising the probes of Cantor as suggested by the Office, this would still fail to result in the invention as claimed.

As used in the specification and the pending claims, "[t]he phrase 'biopolymer subunit precursor' refers to a reactive biopolymer subunit that can add to a growing chain of biopolymer subunits." The instant claims require providing or dispensing *a mixture of two or more different* biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions. Thus, the claims require *a mixture of two or more different* reactive biopolymer subunits that can add to a growing chain of biopolymer subunits, an element which is neither taught nor suggested by the addition of a dimer (a single reactive biopolymer subunit) to a growing biopolymer.

The differences between the cited references and the instant claims with respect to the synthesis process are readily apparent by comparing the disclosure of Baldeschwieler with the claims as described in the instant application.

By way of example, Baldeschwieler indicates at page 13, lines 12-25 that:

> In every coupling cycle, for each address on the array a number is assigned to indicate the correct synthon to be added. During the reagent delivery process, the stage rasters through the addresses of the array. Tetrazole is first applied to the substrate. At each address an additional offset motion is applied to bring the correct phosphoramidite jet (A, C, G or T) in line. One or more droplets of the phosphoramidite are then dispersed. Subsequent to this a second offset motion is employed to bring the tetrazole jet in line with the address. After dispersal of the tetrazole reagent, the stage can raster to the next address for a new delivery cycle.

Thus, Baldeschwieler clearly indicates that a single type of phosphoramidite (A, C, G *or* T) is delivered to each address during a particular round of synthesis.

In view of the above remarks, Applicants submit that the combination of Cantor and Baldeschwieler fails to teach or suggest each and every limitation of Claims 1, 4 and 33. As such, a *prima facie* case of obviousness with respect to these claims has not been established.

Since each of Claims 2-3, 5-9 and 34-48 depend ultimately from one of Claims 1, 4 and 33, the above arguments apply equally to the rejection of Claims 2-3, 5-9 and 34-48.

Claims 1-9 and 33-48 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Cantor in view of Baldeschwieler in light of Cheteverin et al. (U.S.

Patent No. 6,103,463, issued August 15, 2000) (hereinafter "Cheteverin").

According to the Office, even if the claims are interpreted to require providing a mixture of two or more different biopolymer subunit precursors to a feature location in a single round of subunit addition, the combination of Cantor, Baldeschwieler and Cheteverin renders the claims *prima facie* obvious. The Applicants respectfully traverse this rejection.

As discussed above, the combination of Cantor and Baldeschwieler fails to teach or suggest providing or dispensing a mixture of two or more different biopolymer subunit precursors to said feature location in at least one round of multiple rounds of subunit additions. Cheteverin fails to cure this deficiency.

According to the Office:

> Cheteverin et al. disclose that rather than having four oligonucleotides that differ in one position and are immobilized in four separate areas of a comprehensive array, it may be convenient to immobilize "all of these four oligonucleotide in **one area**...[t]hus, instead of having the sequence 'AAAAAAA", "AAATAAA", AAAGAAA", and "AAACAAA" in separate areas, a comprehensive array might be obtained if they are contained in the same area...[t]his would be analogous to having in this area an oligonucleotide with one position that is degenerate."

(Office Action, pages 7-8, emphasis in original).

Based on the above, the Office concludes that "[c]learly, synthesizing a plurality of oligonucleotides in one area, wherein one position is degenerate will result in the dispensing of different nucleotides in the same area (such as A, T, G, and C) in a single pass of nucleotide additions, rendering the instant invention as claimed *prima facie* obvious over the cited references." (Office Action, page 8).

The Applicants respectfully disagree with the Office's characterization of Cheteverin. Specifically, Applicants find no discussion in Cheteverin of "*synthesizing* a plurality of oligonucleotides in one area, wherein one position is degenerate" as suggested by the Office. As indicated above, Cheteverin merely states that "it may be convenient to *immobilize* all of these four oligonucleotides in one area."

(Cheteverin et al., column 12, emphasis added). This language provides no teaching or suggestion to provide (or dispense) a mixture of two or more different biopolymer subunit precursors to a feature location in at least one round of multiple rounds of subunit additions. In fact, the language suggests that the oligonucleotides are deposited intact to an area of the array rather than synthesized via multiple rounds of subunit deposition. This complete lack of disclosure with respect to a required claim element cannot be taken as a teaching or suggestion to include the element.

In view of the above, Applicants submit that the Office has failed to establish a *prima facie* case of obviousness with respect to Claims 1-9 and 33-48. Reconsideration and withdrawal of the rejection of Claims 1-9 and 33-48 under 35 USC § 103(a) are thus respectfully requested.

CONCLUSION

In view of the remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078, order number 10030511-1.

Respectfully submitted,

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